

2.0 RESPONSE

2.1 CHANGE OF APPLICANTS' REPRESENTATIVE

Applicants note for the record that representation of this matter has recently been transferred to the undersigned representative. Authorization for the transfer of this matter to the undersigned's firm was granted and the representative submitted a revocation of power of attorney, a new power of attorney, and a change of customer number/correspondence address to formalize this change of representation on June 29, 2005. Acceptance of this change of address was recorded in the Office on July 21, 2005.

The new attorney docket number for this case is 36697.7, and Applicants appreciate the Examiner's so noting of this in all subsequent communication with the undersigned representative.

Likewise, should the Office or the Examiner-in-Charge of this application have any questions, the Applicants' new undersigned representative may be contacted at the following address:

Mark D. Moore, Ph.D.
HAYNES AND BOONE, L.L.P.
901 Main Street, Suite 3100
Dallas, Texas 75202-3789
Telephone: 713/547-2040
Facsimile: 214/200-0853

2.2 STATUS OF THE CLAIMS

Claims 110-114, 116-117, 120-123, 125, 152-211 were pending at the time of the Action.

Claims 110-114, 116-117, 120-123, 125, 152-180, 193, and 206-211 have been canceled herein without prejudice and without disclaimer, as being drawn to the non-elected invention.

Claims 181-192, 194-205, and 210-211 were examined on the merits in the present Action.

No claims have been amended herein.

Claims 212-221 have been added herein.

Claims 181-192, 194-205, and 212-221 are now pending in the application.

Applicants appreciate the Examiner's finding that no claims are rejected under 35 U. S. C. §§ 101 or 112, second paragraph, and address the remaining rejections of record in the following remarks:

2.3 SUPPORT FOR THE CLAIMS

Support for each of the pending claims, including new claims 212-221 can be found throughout the original claims, Specification and figures as filed. Certain claims have been drafted to incorporate the helpful suggestions of the Examiner as suggested in the Action, and to more clearly and distinctly point out that which Applicants regard as their invention. It will be understood that no new matter is included within any of the newly-submitted claims. Applicants authorize any additional fees necessitated by the presently added claims to be deducted from Applicants' Representatives' Deposit Account as noted above.

2.4 RESPONSE TO OFFICIAL ACTION

Applicants incorporate herein by reference all arguments and reasoning presented in the earlier responses on record in the pending matter. It is respectfully submitted that the pending claims are fully enabled by the specification, that all pending claims are definite, and that all claims are free of the cited prior art. Applicants believe that the claims are acceptable under all sections of the Statutes and are now in conditions for ready allowance, and that all of the concerns of the Examiner have been resolved. Applicants respectfully request, therefore, the withdrawal of all rejections and that a Notice of Allowance be issued in the case with all due speed. However, Applicants note for the record their explicit right to re-file claims to one or more aspects of the invention as originally claimed in one or more continuing application(s) retaining the priority claim of the present case.

2.5 THE OBJECTION TO THE SPECIFICATION UNDER 37 C. F. R. § 132 IS MOOT.

The specification was objected to under 37 C. F. R. § 132, allegedly for containing new matter in view of claims 210-211. (Action at page 5)

Applicants respectfully traverse. However, the rejection of these claims is now moot in view of the present amendment. Applicants respectfully request that the objection be withdrawn in view of same.

2.6 THE REJECTION OF CLAIMS 210-211 UNDER 35 U. S. C. § 112, 1ST PARAGRAPH, IS MOOT.

Claims 210-211 were rejected under 35 U. S. C. § 112, 1st paragraph, allegedly for lacking written description. (Action at page 4)

Applicants respectfully traverse. However, the rejection of these claims is now moot in view of the present amendment. Applicants respectfully request that the rejection be withdrawn in view of same.

2.7 THE REJECTION OF CLAIMS 210-211 UNDER 35 U. S. C. § 102(E) AND (F) IS MOOT.

Claims 210-211 were rejected under 35 U. S. C. § 102(e) and (f), allegedly as being anticipated by Elliott (U.S. Patent 6,090,400). (Action at pages 6-7)

Applicants respectfully traverse. However, the rejection of these claims is now moot in view of the present amendment. Applicants therefore request that the rejection be withdrawn in view of same.

2.8 THE VARIOUS REJECTIONS OF CLAIMS UNDER 35 U. S. C. § 103(A) ARE IMPROPER.

The Office continues to maintain its rejections of various claims allegedly due to a prima facie case of obviousness over a variety of disparate references.

To make its case for obviousness, the Office has relied upon a total of eleven references collected in various combinations to form the bases for nine separate §103 rejections. The eleven references are: (1) Rayat *et al.*, (2) Elliott *et al.*, (3) Brandhorst *et al.*, (4) Clark *et al.*, (5) Maysinger

et al., (6) Saura *et al.*, (7) Pu *et al.*, (8) Boss *et al.*, (9) Champion *et al.* (10) Nielsen *et al.*, and (11) Kallmann *et al.* The nine separate rejections are summarized each in turn here:

Claims 194-197 were rejected under 35 U. S. C. § 103(a) allegedly as being legally obvious over Rayat et al. in view of Nielsen et al, Kallmann et al, and Elliott et al. (Action at page 9)

Claims 194-197 were rejected under 35 U. S. C. § 103(a) allegedly as being legally obvious over Rayat et al. in view of Nielsen et al, and further in view of Brandhorst et al. (Action at page 9)

Claims 194-195, 197-198 and 202 were rejected under 35 U. S. C. § 103(a) allegedly as being legally obvious over Rayat et al. in view of Nielsen et al, and further in view of Clark et al. and Maysinger et al. (Action at page 10)

Claims 194-195, 197-198 and 202-203 were rejected under 35 U. S. C. § 103(a) allegedly as being legally obvious over Rayat et al. in view of Nielsen et al, Clark et al. and Maysinger et al., and further in view of Saura et al. (Action at page 11)

Claims 194-195, 197 and 204 were rejected under 35 U. S. C. § 103(a) allegedly as being legally obvious over Rayat et al. in view of Nielsen et al, and further in view of Boss et al. and Champion et al. (Action at page 14)

Claims 181-182, 184, and 186 were rejected under 35 U. S. C. § 103(a) allegedly as being legally obvious over Rayat et al. in view of Nielsen et al., Clark et al. and further in view of Boss et al., and Champion et al. (Action at page 16)

Claims 181-184 and 186 were rejected under 35 U. S. C. § 103(a) allegedly as being legally obvious over Rayat et al. in view of Nielsen et al., Boss et al., and Champion et al., and further in view of Brandhorst et al. (Action at page 17)

Claims 181-182, 184-186, and 190 were rejected under 35 U. S. C. § 103(a) allegedly as being legally obvious over Rayat et al. in view of Nielsen et al., Boss et al., and Champion et al., and further in view of Clark et al. and Maysinger et al. (Action at page 18)

Claims 190 and 191 were rejected under 35 U. S. C. § 103(a) allegedly as being legally obvious over Rayat et al. in view of Nielsen et al., Boss et al., and Champion et al., and further in view of Saura et al. (Action at page 21)

Applicants respectfully traverse and request that each of the rejections be withdrawn for the reasons discussed in detail hereinbelow:

2.8.1 THE CITED REFERENCES ARE NOT PROPERLY COMBINED.

Each of the prior art rejections remaining in the present case represents a random combination of three, four, or five disparate references, each one of which is said to suggest one or two elements of various pending claims. It is these combinations that are relied upon to deny Applicants allowance of the pending claim based upon the assertion that the combinations are in fact examples of proper *prima facie* obviousness.

The M. P. E. P. (particularly in section 2143.01), 37 C. F. R., 35 U. S. C. §103, and the overwhelming precedent in the case law, however, have made it clear that a finding of obviousness under 35 U. S. C. §103 requires a determination of both the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed subject matter and the prior art, and whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere*, 383 U.S. 1, 148 USPQ 459 (S. Ct. 1966). The relevant inquiry is whether the prior art suggests the invention and whether the prior art would have provided one of ordinary skill in the art with a reasonable expectation of success. *In re O'Farrell*, 7 USPQ2d 1673 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art and not in the Applicant's disclosure. *In re Vaeck*, 20 USPQ 1438 (Fed. Cir. 1991).

The question of whether a combination of references provides the requisite level of motivation has also been clearly answered by the Courts. "There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998). In this case, while the combination of the references taught every element of the claimed invention, a rejection based on a *prima facie* case

of obviousness was held improper, because there was *no specific motivation to combine* the various references. In *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999), the Court also addressed this issue: "The level of skill in the art cannot be relied upon to provide the suggestion to combine references." Likewise in *Linter*, the Courts stated: "In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." *In re Linter*, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972).

The M. P.E. P. itself clearly summarizes the standard that has been set down in case law: "Obviousness can only be established by *combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art.*" (Emphasis added).

"The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000). See also *In re Lee*, 277 F.3d 1338, 1342-44, 61 USPQ2d 1430, 1433-34 (Fed. Cir. 2002) (discussing the importance of relying on objective evidence and making specific factual findings with respect to the motivation to combine references); *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In alleging that the claimed invention is obvious over the various combinations of three or more cited references, the Office appears to have identified and extracted claimed elements from the references, but appears to have ignored the legal standard governing the combination of references under 35 U. S. C. § 103.

While it is well-established that Office may combine the disclosure of two or more prior art references in order to establish *prima facia* obviousness, it is also well-established that in order to do so, there **must** be some *suggestion* or *motivation* for doing so, found either in the references themselves or in a knowledge generally available to one of skill in the art. See *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988):

In *Fine*, the claims were directed to a system for detecting and measuring minute quantities on nitrogen compounds comprising a gas chromatograph, a converter which converts nitrogen compounds into nitric oxide by combustion, and a nitric oxide detector. The primary reference disclosed a system for monitoring sulfur compounds comprising a chromatograph, combustion means, and a detector, and the secondary reference taught nitric oxide detectors. While the Examiner and Board asserted that it would have been within the skill of the art to substitute one type of detector for another in the system of the primary reference, the Court, however, found there was no support for this conclusion and reversed.

The Federal Circuit has made it clear that "the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references" (*In re Dembicza*k, *supra* at 1617). The Office must specifically identify "the reasons one of ordinary skill in the art would have been motivated to select the references and combine them" (*In re Rouffet*, 47 USPQ2d 1453, 1459 (Fed Cir. 1998). "Combining prior art references without evidence of such a suggestion, teaching,

or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability – the essence of hindsight" (*In re Dembicza*k, *supra* at 1617).

Because the claims in the case particularly point out the distinct features of the inventive methods disclosed in the Specification, and because each of such claims is clearly distinguished over the previously cited art (either alone or in combination) Applicants further believe that, as a matter of law, the rejection advanced under 35 U. S. C. § 103 cannot stand.

Applicants urge the application of the standard held in the case of *In re Vaeck*, 20 U.S.P.Q. 1438 (Fed. Cir. 1991), in which the Federal Circuit stated that in order for an examiner to make out a *prima facie* case of obviousness two things must be shown:

- (1) That the prior art would have suggested to those of ordinary skill in the art that they should make the claimed invention; and
- (2) That the prior art must demonstrate a reasonable expectation of success of the invention.

Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the Applicant's disclosure (emphasis added).

Furthermore, in the case of *In re Dow Chemical Co.* (837 F. 2d 469, 5, U.S.P.Q.2d 1529, Fed. Cir. 1988) the court held that an "obvious-to-experiment" standard is not an acceptable alternative for obviousness, and that there must be a reason or suggestion in the art, *other than* the knowledge learned from the Applicant's disclosure.

In the instant case, however, there is neither the suggestion nor the reasonable expectation of success. Even if one could somehow postulate that one or more of the cited references might suggest that a method similar to the disclosed invention might, in an abstract sense, be *plausible*, there is certainly no teaching or suggestion as to how one would go about

developing the methods of the present invention, nor is there any suggestion in the cited references, either alone or in combination, that such an approach would be successful. These references neither alone nor in the various combinations presented provide either the teaching, the motivation, or the expectation of success for methods of preparing xenotransplantable porcine islets that comprise the steps of harvesting the pancreas of a piglet having an age of between -20 to +10 days relative to full term gestation, exposing the harvested pancreas to (a) nicotinamide, (b) a trauma protecting agent, and (c) a quinolone antibiotic, and then extracting pancreatic .beta. islet cells from the harvested pancreas under conditions effective to obtain the xenotransplantable islet.

Likewise there is no motivation or teaching that such methods could be used to achieve islet cells that when provided to an animal could be utilized to treat, prevent, ameliorate, or reduce the progression of a disease caused by an islet cell deficiency in an animal.

Furthermore, Applicants submit that *the combination of references relied upon by the Examiner also clearly fails to satisfy the tripartite test of In re O'Farrell (7 U.S.P.Q.2d 1673, 1680, Fed. Cir. 1988)*. In *O'Farrell*, the Court held that in order for a reference or references to obviate an invention, it must be shown that the reference(s) contains:

- (1) Detailed enabling methodology for practicing the claimed invention;
- (2) A suggestion for modifying the prior art to practice the claimed invention; and
- (3) Evidence suggesting that the invention would be successful.

In the present case (1) none of the myriad of references provides any teaching relevant to the question of how one of skill would proceed to prepare such xenotransplantable islet cells, and most certainly does not provide any “detailed enabling methodology” for practicing the claimed invention; (2) none of the cited references in the present case provides any suggestion for

combining the teachings of the various references in any combination or for modifying any of these prior disclosures in a manner that would allow one to arrive at the present invention; and (3) none of the references provides evidence that the present invention would be successful. Clearly the rejection is improper as it fails the tripartite test of *In re O'Farrell*.

Applicants assert that any combination of the cited references is, at best, merely an invitation for further experimentation in the field, and at most, an “obvious-to-try” situation. However, there is *no* reasonable expectation of success, *nor* is there the motivation or teaching to guide a skilled artisan how to achieve such success. The Federal Circuit, in the case of *In re Geiger* (815 F.2d. 686, 2 U.S.P.Q.2d 1276, Fed. Cir. 1987), held that obviousness cannot be established by combining the teachings of the prior art to produce a claimed invention, absent some teaching, suggestion or incentive supporting the combination. Again, Applicants believe that the rejection fails the test of *In re Geiger*.

Further, in *Amgen v. Chugai Pharmaceutical Co. Ltd.*, (927 F. 2d 1200, 18 U.S.P.Q. 2d 1016, 1022, Fed. Cir. 1991) the Court affirmed that obviousness under 35 U. S. C. § 103 is a question of law, and that both the suggestion and the expectation of success must be founded in the prior art, and not in the Applicants’ disclosure. Because the suggestion and expectation of success are absent in the cited art, Applicants assert that the rejection also fails the test of *Amgen v. Chugai Pharmaceutical Co. Ltd.*

Therefore, as a matter of both fact and law, Applicants believe that the obviousness rejection over any of the cited references, either alone or in any combination, or when taken alone or together in view of the secondary, tertiary, or quaternary references of record is improper and must be withdrawn.

As such, Applicants believe that each of the remaining obviousness rejections is overcome, and respectfully request that each of the rejections be withdrawn for these reasons in general, and for the following reasons in specific:

2.8.2 THE FACT THAT REFERENCES *CAN* BE COMBINED OR MODIFIED IS NOT SUFFICIENT TO ESTABLISH *PRIMA FACIE* OBVIOUSNESS

Turning again to the M. P. E. P.'s exhaustive teaching on the combinability of prior art references for obviousness determinations, "(T)he mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990) Although a prior art device "may be capable of being modified to run the way the apparatus is claimed, there must be a suggestion or motivation in the reference to do so." 916 F.2d at 682, 16 USPQ2d at 1432.). See also *In re Fritch*, 972 F.2d 1260, 23 USPQ2d 1780 (Fed. Cir. 1992)."

Beginning with the first office Action, we summarize the Office's ongoing position with respect to obviousness:

(1) Rayat *et al.*, is said to teach "a method of preparing porcine islets cells as potential source (*sic*) for transplantation into humans comprising harvesting the pancreas from neonatal piglets at 1-3 days, extracting pancreatic islet beta cells, and culturing the islet cells with nicotinamide and bovine serum albumin (trauma-protecting agent) under sterile condition (*sic*) (free of microbial (*sic*) by including penicillin and streptomycin in the medium, paragraph bridging pages 1406-07." (Office Action dated 7/30/03, page 7)

Applicants note for the record, however, that this reference does *not* teach that BSA is a "trauma protecting agent." In fact, the reference doesn't even mention the words "trauma protecting agent," even though the Examiner has apparently concluded otherwise. Despite the Office's characterization of the reference, it says nothing about the significance of BSA in the culture medium, nor does it teach or suggest that any "trauma protecting agent" is required or desired in the

practice of its teachings. Moreover, the reference *does not teach or suggest* the use of “trauma protecting agents” are desirable in the preparation of porcine xenotransplants, and it certainly *does not teach or suggest* that a class of anesthetic agents, (and particularly phospholipase A2 inhibitors), are either desirable or useful in processes for the preparation of porcine islets. Finally, the reference does not teach or suggest any use of phospholipase A2 inhibitors, much less the use of lignocaine in specific.

The primary reference relied upon for all of the obviousness rejections fails to teach or suggest features of the claimed invention, and certainly *does not provide the requisite expectation of success* for modifying the reference in such a fashion that would result in the present invention. Based upon this fact alone, the combination of the references using Rayat *et al.* as a primary reference, is both improper as a matter of law, and inaccurate as a matter of fact.

(2) Elliott *et al.* is said to teach “a method of preparing a xenotransplantable porcine islet (pig to mouse, column 2, lines 5-6) comprising harvesting the pancreas of piglets at near full term gestation (the full term for piglet is around 115 days, thus, -20 to +10 days is at or near the full term gestation, and treating the islet cells with nicotinamide and any compound exhibiting similar growth promoting and cytoprotective effects (column 1, lines 24-30). Elliot also teaches mechanically reducing the harvested pancreas (diced) in the presence of cytoprotective agents (column 2, lines 23-26).”

As noted below, the patent to Elliott is commonly owned with the present application, and submission of a declaration under §1.131 is sufficient to remove this reference entirely as prior art. However, the patent to Elliott does not teach or suggest the particular features claimed in the present application, nor does it provide a motivation to combine its teachings with those of Rayat, or any of the other cited references, nor does it contain the requisite expectation of success for arriving at the particular features of the present invention. As such, Applicants argue that the references has been improperly combined with secondary references, and cannot properly be relied upon for obviousness-type prior art.

(3) Brandhorst *et al.* is said to teach “that a barrier for successful islet isolation is the intrinsic fragility of islets during pancreas digestion and using human liberase could double the yield of islet cells compared to collagenase” (Office Action dated 7/30/03, page 10)

(4) Clark *et al.* is said to teach “that a barrier for successful islet isolation is the intrinsic fragility of islets during pancreas digestion and using human liberase could double the yield of islet cells compared to collagenase” (Office Action dated 7/30/03, page 10)

(5) Maysinger *et al.* is said to teach “culturing mammalian islet cells in general in the presence of IGF-1 (page 4, line 30) and one or more growth factors (*sic*) having anti-apoptosis effect (*sic*) on islet cells (trauma preventing agent, abstract). Evidently the skilled artisan does not discriminate among the species of the mammalian (*sic*) for culture conditions of islet cells. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by Rayat *et al.*, Clark *et al.*, and Maysinger *et al.* by simply including IFH-1 and HAS and adding trauma protecting agent (*sic*) during the mechanical disassociation of pancreas with a reasonable expectation of success.” (Office Action dated 7/30/03, page 11) The Action goes on to state “The ordinary skilled artisan would have been motivated to modify the claimed invention because the modified method enhances the viability and sustained survival of *ex vivo* cultured islet cells.” (Office Action dated 7/30/03, page 12, emphasis added).

Applicants respectfully traverse, and note that the last sentence of this section of the Office Action is clear example of hind-sight reconstruction utilized to tie the various disparate references together. The Office considers that one of skill in the art would have been motivated ”to modify the claimed invention” because the modified method “enhances viability and sustained survival....”. This is an improper standard, which is clearly at odds with the Statute and the case law. The question is not whether one would have been motivated *to modify the claimed invention*; the standard is whether or not one would have been motivated **to modify the teachings of the prior art!** One would only have known that the claimed method was superior to the prior art, after they read Applicants’ disclosure. That is clear hindsight reconstruction, and it is impermissible under the Statute. The relevant question for obviousness is, whether or not a skilled artisan would have found an expectation in the prior art that the combination of those references would achieve the claimed results. The standard is not whether one would have been motivated to modify *Applicants’*

invention to arrive at the prior art! When one knows the answer in advance, it is always much easier to postulate the correct question.

For these reasons, these three references are disqualified as prior art because they each lack the relevant teaching or suggestion, the motivation to combine them with one or more secondary references, and most importantly, they lack the expectation of success as has now been shown by Applicants' disclosure. Because the incorrect standard has been applied for the combinability of these references in a hind-sight approach, Applicants respectfully request that the rejection in view of each of these references be withdrawn.

Turning to reference (6), Saura *et al.* is said to teach "that the GPE does have the biological activity of full-length IDF-I in the brain tissue (see particularly Introduction). Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by Rayat *et al.*, Clark *et al.*, and Maysinger *et al.* by simply substituting full length IFG-1 with the GPE tripeptide with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because it has been proven that GPE has the biological activity of IGF-1 and has a smaller size (easier for delivery), thus providing additional means for similar biological activity." (Office Action dated 7/30/03, pages 12-13, emphasis added).

Once again, Applicants respectfully traverse, and note this is another clear example of hind-sight reconstruction. The Office considers that one of skill in the art would have been motivated "to modify the claimed invention" because the modified method "has been proven that GPE has the biological activity of IGF-1 and has a smaller size". This is an improper standard, which is clearly at odds with the Statute and the case law. The question is not whether one would have been motivated *to modify the claimed invention*; the standard is whether or not one would have been motivated **to modify the teachings of the prior art!** One would only have known that the claimed method was superior to the prior art, after they read Applicants' disclosure. Again, this is a clear example of hindsight reconstruction, which is impermissible under the Statute. The relevant

question for obviousness is, whether or not a skilled artisan would have *found an expectation* in the prior art to achieve the superiority of the invention, without having read Applicants' disclosure.

The Saura reference discloses that GPE can prevent neuronal death in the hippocampus injured by NDMA via unique receptors expressed in the hippocampus. A skilled artisan in the field of pancreas islet cell preparation would not have been motivated to use a brain-active compound in an in vitro culture medium to improve the growth and survival of islet cells, because it is not expected that pancreatic islet cells contain hippocampal-specific receptors!

For this reason, the reference is disqualified as prior art because it lacks the relevant teaching, suggestion, motivation to combine, and expectation of success as has now been shown by Applicants' disclosure. Applicants respectfully request that the rejection be withdrawn.

With respect to reference (7), Pu *et al.* is said to teach "that the addition of lignocaine in isolated rabbit heart tissue culture could restore the contractility of myocardiocytes after minor traumatic injury (myocardial contusion), and thus lignocaine could be used as a therapeutic agent for tissue recovery from minor trauma (abstract, and Section 5)" (Office Action dated 7/30/03, page 13)

Again, Applicants respectfully traverse, and Applicants' representative is again utterly perplexed by the citation of this reference in the present case, and it's alleged proper combinability with the other references listed to arrive at a finding of obviousness for the claimed methods involving methods of preparing pancreatic xenotransplants.

Pu *et al.* uses lignocaine in an *ex vivo* heart perfusion system with a view to using lignocaine as a treatment for damage caused by heart attacks *in vivo*. The effect that lignocaine has in the perfused hearts is described on page 1077 of the reference, which indicates that the results those authors observed related to *cardiac-specific* cellular physiology. The reference teaches or suggests NOTHING about isolating pancreatic islet cells, nothing about xenotransplantation of porcine

pancreatic cells in a human, and nothing about modifying any of the other cited references to arrive at the present invention. To suggest that one of skill in the art would have been “motivated to modify the claimed invention” because lignocaine was shown to be effective in restoring damage to cardiac tissues is completely without scientific or legal foundation. Again, the question is not whether one of skill in the art would have been motivated *to modify the claimed invention* to explain aspects of the prior art; the standard is whether or not one would have been motivated **to modify the teachings of the prior art to render obvious the present invention.**

For this reason, Applicants urge that the rejection be withdrawn and that the claims proceed to immediate allowance.

Turning now to reference (8), Boss *et al.* is said to teach “that quinoline (*sic*) antibiotics is (*sic*) useful in preventing mycoplasmal contamination....” (Office Action dated 7/30/03, page 14)

Additionally, reference (9), Champion *et al.*, is said to teach “that ciprofloxacin (*sic*) ciproxin belongs to quinoline (*sic*) antibiotics” (Office Action dated 7/30/03, page 14) The Action goes on to state, “it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by Rayat *et al* by including ciproxin in the culture medium for preventing mycoplasmal contamination....”

Yet again, Applicants respectfully traverse, and point out that hindsight reconstruction is once again being incorrectly applied as the standard for trying to “explain” the prior art by using the results of the present invention to do so.

Boss *et al.* suggests that a reagent comprising tylosin (a non-quinolone antibiotic!) and optionally one or more antibiotics (some of which happen to be quinolones) is useful in treating mycoplasmal contamination. One of skill in the art, therefore, reading Boss *et al.* would have been motivated to use *tylosin* as a primary antimycoplasmal agent, and not motivated to select a specific chemically-related subfamily of antibiotics (*i.e.*, quinolones) to improve preparation of pancreatic xenotransplanted islets. The mere fact that these references disclose known antibiotics (some of

which are quinolones) is insufficient reasoning (either scientifically or legally) to suggest that the render obvious the present invention, and for that reason, the Applicants request that the reference be removed as prior art, and that the rejection be immediately withdrawn.

Finally, considering references (10) and (11), Nielsen *et al.* is said to “supplement Rayat et al by teaching the mechanisms and clinical use of nicotinamide in protecting the pancreatic beta cells. Nielsen *et al* teach that NA could inhibit cytotoxicity caused by nitro oxide (*sic*) and other free radicals on beta cells (which are often seen in trauma) such as evidenced by (11) Kallmann *et al*, as well as influence several of the putative intracellular molecular events following immune attack on the beta cells such as evidenced by Elliott *et al.*” (Office Action dated 5/20/04, page 13)

Applicants again respectfully traverse. Nielsen discloses that nicotinamide can inhibit cytokine activity (*i.e.*, immune mediated cytotoxicity) *in vivo*. This activity is completely different to the endogenous cellular cytotoxicity of an *in vitro* system. The references teaches or suggests nothing about xenotransplantation of pancreatic islets, nor about how to prepare them, or why the use of nicotinamide in such a method would be either successful or desirable. As such, a skilled artisan would *not* have been motivated to utilize the teachings of Nielsen to substitute nicotinamide into the culture medium of Rayat *et al.* and/or the other secondary references to arrive at the present invention. Therefore, the citation of these two references as prior art, either alone or in any combination with the remaining references of record is improper. Applicants respectfully request, therefore, that the rejection be withdrawn in view of these two references.

In summary, the cited references are not properly combinable, do not teach or suggest the invention, and do not provide a reasonable expectation of success to the skilled artisan. The rejection of claims under 35 U. S. C. § 103(a) in view of the various combinations of these reference has been overcome. Applicants therefore respectfully request the withdrawal of these rejections, and that the claims proceed to allowance with all due course.

2.8.3 THE CITED COMBINATIONS OF REFERENCES DO NOT PROVIDE A REASONABLE EXPECTATION OF SUCCESS TO ESTABLISH *PRIMA FACIE* OBVIOUSNESS

In *Levengood*, it was decided that a statement that modifications of the prior art to meet the claimed invention would have been “well within the ordinary skill of the art at the time the claimed invention was made” simply because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). See also *In re Kotzab*, 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1318 (Fed. Cir. 2000) In this case, the Court reversed an obviousness rejection involving a technologically-simple concept because there was no finding as to the principle or specific understanding within the knowledge of a skilled artisan that would have *motivated* the skilled artisan to make the claimed invention (Emphasis added). *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999) In this case, it was decided that “the level of skill in the art cannot be relied upon to provide the suggestion to combine references.” (Emphasis added).

2.9 THE PROVISIONAL REJECTION OF CLAIMS 194-195, AND 197-198 FOR OBVIOUSNESS-TYPE DOUBLE PATENTING IS NOTED.

Claims 194-195 and 197-198 were provisionally rejected for obviousness-type double patenting over commonly-owned U. S .patent 6,146,653. (Action at page 23)

Applicants respectfully traverse. However, they note for the record that the cited patent and the present application are commonly owned, and as such, the rejection may be overcome by submission of an executed terminal disclaimer in compliance with 37 C. F. R. § 1.321(b)(c) and (d), disclaiming the terminal part of the statutory term of any patent granted on the instant

application, which would extend beyond the expiration date of the full statutory term defined in 35 U. S. C. §§ 154 to 156 and 173, as shortened by any terminal disclaimer, of the issued U. S. patent which is commonly owned with the present application.

However, Applicants note that the filing of a terminal disclaimer to obviate a rejection based on non-statutory double patenting is not an admission of the propriety of the rejection. *Quad Environmental Technologies Corp. vs. Union Sanitary District*, 20 USPQ 2d 1392 (Fed. Cir. 1991).

The Court in *Quad* indicated that:

"filing of a terminal disclaimer simply serves the statutory function of removing the rejection of double patenting, and raises neither a presumption nor estoppel on the merits of the rejection."

Applicants elect to defer submission of that paper until such time as the claims are allowed in the present case. Applicants therefore request that the Rejection be held in abeyance until a notice of allowability is forthcoming.

2.10 THE PROVISIONAL REJECTION OF CLAIMS 210-211 FOR OBVIOUSNESS-TYPE DOUBLE PATENTING IS MOOT.

Claims 210-211 were provisionally rejected for obviousness-type double patenting over U. S. patent 6,146,653 and U.S. patent 6,090,400. (Action at page 24)

Applicants respectfully traverse. However, the rejection of these claims is now moot in view of the present amendment. Applicants therefore request that the Rejection be withdrawn in respect of same.

2.11 THE OBJECTION TO CLAIMS 189, 192, 201 AND 205 IS OVERCOME.

Claims 189, 192, 201, and 205 were objected to for allegedly being allowable if re-written in independent form including the limitations of the base and intervening claims. (Action at page 24)

Applicants respectfully traverse. However, as Applicants appreciate the finding of the Examiner that the subject matter of these claims is patentable and free from other rejection, Applicants have introduced herein new claims 212-215 to correspond to the allowable subject matter of these claims, respectively. Applicants therefore request that the Objection be withdrawn and that these claims proceed to allowance.

2.12 REQUEST FOR EXAMINER INTERVIEW

As requested above, and pursuant to M. P. E. P. § 713.01 and 37 C. F. R. §1.133, should the Examiner have any concerns about the allowability of any pending claim or have any question about the arguments, remarks, and/or evidence presented herein, after having an opportunity to review and consider them, Applicants respectfully request that the Examiner contact the undersigned representative for the purpose of scheduling an Interview with the Examiner-in-Charge, Supervisory Examiner Shukla, a TC1600 Practice Specialist (for example, Ms. Deborah Reynolds, if available) and Applicants' undersigned representative *prior to the issuance of any successive Action on the merits* to discuss all pending claims, and to address any particular remaining issues in the mind of Examiner Li once she has had the opportunity to review the present amendment and consider the remarks in this response.

2.13 CONCLUSION

It is respectfully submitted that the pending claims are fully enabled by the Specification, that all pending claims are definite, and free of the cited prior art. Applicants believe that the claims are acceptable under all sections of the Statutes and are now in conditions for ready allowance, and that all of the concerns of the Examiner have been resolved. Applicants further respectfully request, therefore, the withdrawal of all rejections and that a Notice of Allowance be issued in the case with all due speed. However, Applicants also note for the record their explicit right to re-file claims to one or more aspects of the invention as originally claimed in one or more continuing application(s) retaining the priority claim from the present and parent cases.

Should the Examiner have any questions, a telephone call to the undersigned Applicants' new representative would be appreciated.

Respectfully submitted,



Mark D. Moore, Ph.D.
Registration No. 42,903

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HAYNES AND BOONE, LLP
901 Main Street, Suite 3100
Dallas, Texas 75202-3789
Telephone: 713-547-2040
Facsimile: 214 200-0853
36697.7

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